Politecnico di Torino
Department of Mechanical and Aerospace Engineering

Master Degree in BIOMEDICAL ENGINEERING

Designing injectable supramolecular formulations for the localized delivery of nucleic acids

INTRODUCTION

Hydrogels are soft hydrophilic three-dimensional networks of cross-linked macro-molecules. Many natural and synthetic polymers can be used as forming components of hydrogels for biomedical applications. Covalently cross-linked hydrogels exhibit stable water-based networks, which are often used to produce cellularized substrates for tissue engineering/regenerative medicine. Chemical hydrogels have also been widely used to release specific drugs, but the formulation and payload release kinetics represent challenging aspects to be finely controlled. Differently, physically cross-linked hydrogels are developed by relying on reversible interactions (i.e., hydrogen, Van der Waals, hydrophobic or ionic bonds), thus widening the possibilities to engineer release kinetics and degradation/dissolution profiles. Hence, hydrogels based on reversible bonds are often preferred to design drug releasing systems, with the additional advantage of providing a protective environment to the encapsulated cargo and minimizing the risks for drug/biomolecule degradation/denaturation due to the mild gelation conditions. However, the design of stable systems showing a sol-to-gel transition driven by physical interactions is not simple, since phase separation phenomena or weak network formation represent realistic issues. A possible strategy to obtain tunable physical hydrogels consists in inducing the sol to gel transition by exploiting specific interactions which can arise among the hydrogel components and finally lead to the formation of supramolecular (SM) structures. In SM chemistry, cyclodextrins (CDs) are widely employed and investigated molecules, owing to their capability to form SM interactions with specific moieties. In this regard, the use of custom-made materials, such as those of the poly(ether urethane) family, could provide significant advantages in terms of versatility of the formulation composition, mechanical properties and stability in water environments. For what concerns hydrogel payload, nucleic acids, such as siRNAs and mRNAs, have tremendous potential for therapeutic applications. However, advancements in this field are limited by the need to engineer optimal carriers for their delivery. If systemically administered these molecules are rapidly degraded, may have off-target silencing, and necessitate high working concentrations. To

overcome these drawbacks, polyplexes based on nucleic acid molecules and a cationic polymer can be embedded into injectable physical hydrogels, providing additional protection to the biomolecules and allowing their local and sustained delivery in the target area.

GOAL of the WORK and ORGANIZATION

This thesis work will aim at the design and thorough characterization of supramolecular poly(ether urethane)-based hydrogels embedding polyplexes prepared starting from nucleic acid molecules and a cationic polymer (both commercially available and custom-made polymers will be tested as polyplex forming material). This work has been developed in the framework of the scientific collaboration between Politecnico di Torino (Prof. Gianluca Ciardelli) and the Ludwig-Maximilians-Universität München, Germany (Prof. Olivia Merkel, https://www.cup.lmu.de/pb/aks/merkel/), that have documented experience in SM hydrogel design and polyplex formulation, respectively. The research work will be conducted at the Ludwig-Maximilians-Universität München under the supervision of Prof. Merkel for around 6 months starting from March 2023. The Master Student will be involved in the design and encapsulation of nucleic acid/cationic polymer polyplexes into SM hydrogels and their thorough physico-chemical (payload release profile, injectability, stability, rheological properties) and biological (cytocompatibility and biological effect of the released cargo) characterization. Before the beginning of the mobility a 2-3 week period at the Biomedical Lab of Politecnico di Torino (sited in Alessandria) could be possibly planned to familiarize with polymer synthesis and SM hydrogel preparation. The candidate will also perform a thorough literature research for all the duration of the thesis project in order to analyze the state of the art.

REQUIREMENTS

1) Availability to spend approx. 6 months in München (Germany).

2) Potential availability to work in the Alessandria's Lab for 2-3 weeks before the beginning of the mobility (to be defined).

3) Candidates having completed all the exams will be given priority during the selection phase.

CONTACT

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